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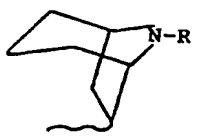
(57) Abstract

Compounds of the formula (I): X-A-Z, and pharmaceutically acceptable salt thereof, wherein Z is of structure (a) or (b), wherein X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring; A is a linking moiety; and R is hydrogen or methyl; having 5-HT_3 receptor antagonist activity.



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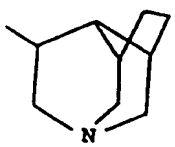

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AZABICYDIC AND AZATRICYDIC DERIVATIVES, PROCESS AND INTERMEDIATES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This invention relates to novel compounds having useful pharmacological properties, to a process for their preparation, and to their use as pharmaceuticals.

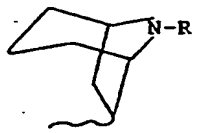
EP-A-158265, EP-A-200444, EP-A-247266, EP-A-235878, EP-A-254584, EP-A-255297, EP-A-289170, EP-A-315390, PCT GB91/00636, PCT/GB91/02173 and PCT/GB91/02210 (Beecham Group p.l.c.), EP-A-158532 (A.H. Robins Company, Inc.), EP-A-67770 (Merrell Toraude et Compagnie), GB 2125398A and GB 2145416A (Sandoz Limited), EP-A-322016 (Duphar international Research B.V.), EP-A-307172 (Eli Lilly and Company), EP-A-323077, EP-A-306148, GB 2208385A and WO91/05783 (John Wyeth and Brother Limited), EP-A-234872 (Adria Laboratories Inc.), EP-A-294292 (Adir et Compagnie), EP-A-339950 (Rorer International (overseas), Inc.), EP-A-309423 (Instituto de Angeli S.p.A.), EP-A-313393 and EP-A-407137 (Yoshitomi Pharmaceutical industries Limited), EP-A-328200 and EP-A-337547 (Merck Sharp and Dohme Limited), EP-A-329932 (Merrell Dow Pharmaceuticals Inc.), WO 90/06039, WO 91/16888 (Rorer International (Overseas), Inc.), EP-A-378111 (Zambon Group S.p.A.), EP-A-403882 (Fujisawa Pharmaceutical Co. Ltd.), EP-A-419397 (A/S Ferrosan) and EP-A-458636 (Kyoma Hakko Kogyo Kabu Shiki Kaisha) and USA Patents 4920219 and 4920227 (Rorer Pharmaceutical Corp.) disclose classes of compounds which have a saturated azabicyclic moiety, such as tropanyl, granatyl or quinuclidinyl, and are 5-HT_3 receptor antagonists.

A class of novel, structurally distinct compounds has now been discovered in which the saturated azabicyclic moiety is 8-azabicyclo[3.2.1]octan-6-yl or 6-azatricyclo[4.3.$0^{4,9}$]decan-8-yl. These compounds have 5-HT_3 receptor antagonist activity.

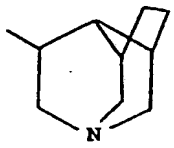
Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:

X-A-Z (I)

wherein Z is of structure (a) or (b):



(a)



(b)

wherein

X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;

A is a linking moiety; and

R is hydrogen or methyl;

having 5-HT_3 receptor antagonist activity.

X may be unsubstituted or substituted, usually by one or more substituents selected from halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, hydroxy, amino, C_{1-6} alkylamino, C_{1-7}

alkanoylamino, or two substituents on X (when fused), may be linked to form a saturated or unsaturated optionally substituted carbocyclic ring.

Heteroatoms for heteroaryl and heterocyclic groups are selected from oxygen, nitrogen and sulphur.

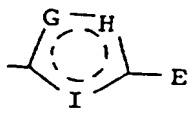
Halo includes bromo, chloro and fluoro.

X may be joined to A by an aromatic carbon atom, or (when X is fused), by a carbocyclic ring carbon atom, or by a heterocyclic ring carbon or nitrogen atom. When X is fused, and A is attached at an aromatic carbon atom, it is preferably attached at the aromatic carbon adjacent a 'fused' carbon atom, which is attached to the heteroatom of a heterocyclic ring in formula (I). Z may be attached to A in a 'spiro' configuration.

X may also be further joined to A as defined in formula (IA) hereinafter, when $Y-R_{10}$ is N-B=N.

Suitable examples of X are as described in the aforementioned patent publications relating to $5-HT_3$ receptor antagonists, the subject matter of which is incorporated herein by reference.

Suitable examples of A include CONH (amide), COO (ester), NHCONH (ureide), CONHCONH (extended ureide), or a group of structure (j):



(j)

wherein the dotted circle represents two double bonds in any position in the 5 membered ring; two of G, H and I are selected from oxygen, sulphur, nitrogen and carbon and the other is oxygen, sulphur or nitrogen; and E is a bond or C_{1-5} alkylene optionally substituted by phenyl or hydroxy; or E is absent and heterocycle in structure (j) is joined to Z in a 'spiro' configuration.

For the avoidance of doubt, the suitable X values in formula (I) which are described in the referenced patent publications, are that part of the structure remaining when the saturated azabicyclic moiety and A (where A is one of the suitable examples listed above), are disregarded.

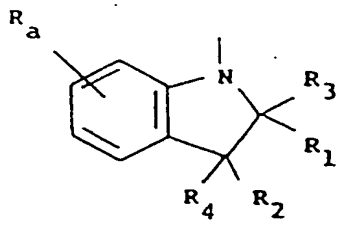
In a particular aspect, the present invention provides a compound of formula (IA), or a pharmaceutically acceptable salt thereof:

$$X_1\text{-CO-Y-Z} \qquad \text{(IA)}$$

wherein

Y is NH or O (or is joined to R_{10} as defined below);

X_1 is a group of formula (a), (b), (c), (d), (e), (f), (g) or (h):



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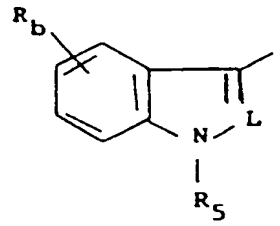

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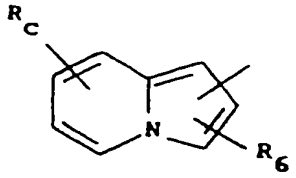

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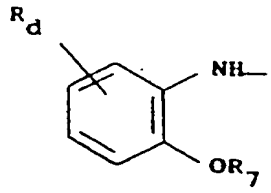

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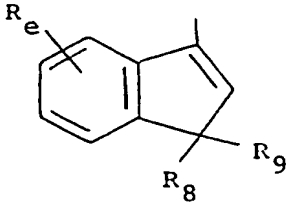

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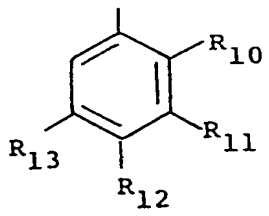

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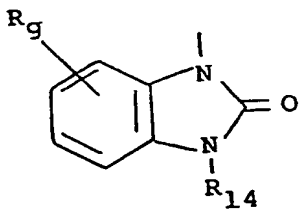

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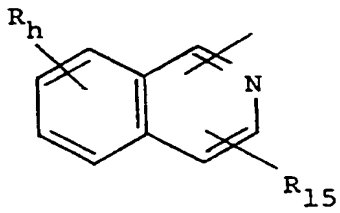


(h)

wherein

R_a to R_e and R_g to R_h are selected from hydrogen, halogen or hydroxy;

R_1 is hydrogen and R_2 is hydrogen or C_{1-4} alkyl; or

R_1 and R_2 together are a bond;

R_3 to R_7 are independently hydrogen or C_{1-6} alkyl; and

R_4 together with R_2 may be C_{2-7} polymethylene or C_{2-6} polymethylene interrupted by an -O- linkage when R_1 is hydrogen;

R_8 and R_9 are independently selected from hydrogen or C_{1-6} alkyl or R_8 and R_9 together are C_{2-6} polymethylene or C_{2-5} polymethylene interrupted by an -O- linkage;

either R_{10} is hydrogen, C_{1-6} alkoxy, C_{3-8} cycloalkyloxy or C_{3-8} cycloalkyl C_{1-4} alkyloxy; or R_{10} is joined to Y so that Y-R_{10} is N-B=N where B is N or CH; and

R_{11} is hydrogen, halo, C_{1-6} alkoxy or C_{1-6} alkyl; or

R_{10} and R_{11} are joined to form $-OCH(R_{15}R_{16})-E-$ wherein E is $(CH_2)_n$, $(CH_2)_pO\ NR_{17}CO(CH_2)m$ wherein n is 1 or 2, p is 0 or 1 and m is 0 or 1 and R_{15}, R_{16} and R_{17} are independently selected from hydrogen or C_{1-6} alkyl;

R_{12} is hydrogen, C_{1-6} alkoxy or; amino optionally substituted by a C_{1-6} alkyl group, or R_{12} is alkanoylamino; and

R_{13} is halo, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio;

R_{14} is hydrogen or C_{1-6} alkyl;

in formula (h):

CO-Y- is in the 1-position and either R_{15} is in the 3-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, phenyl optionally substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups or by C_{4-5} polymethylene or by phenyl, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy or nitro; or

CO-Y- is in the 3-position and either R_{15} is in the 1-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen or C_{1-6} alkoxy;

L is CH or N; and

Z and R are as defined in formula (I).

Examples of moieties in alkyl or alkyl containing groups in Z or in R_1 to R_{15} include methyl, ethyl, n- and iso-propyl,

n-, iso-, sec- and tert-butyl, preferably methyl. Cycloalkyl moieties include C_3, C_4, C_5, C_6, C_7 and C_8 cycloalkyl. Halo moieties include fluoro, chloro, bromo and iodo.

Suitable examples of R_2 and R_4 or R_8 and R_9 when joined include C_2, C_3, C_4, C_5 or C_6 polymethylene, preferably C_2, C_3, C_4 or C_5 polymethylene.

R_a to R_e and R_g to R_h are preferably selected from hydrogen, fluoro, chloro and hydroxy, most preferably hydrogen. R_b may be 5-, 6- or 7-chloro or fluoro.

When X is of sub-formula (a), one of R_1 and R_3 is preferably hydrogen and one or both of R_2 and R_4 (most preferably both) are alkyl groups, such as methyl, or are joined to form C_{2-7} polymethylene; or when one of R_2 and R_4 is hydrogen, the other is preferably ethyl or n- or iso- propyl.

When X is of sub-formula (b), R_5 is preferably hydrogen or a methyl or ethyl group.

When X is of sub-formula (c), one of CO-Y and R_6 is attached at the 1-position and the other is attached at the 3-position as depicted in sub-formula (c), and R_6 is preferably methyl or ethyl.

When X is of sub-formula (d), R_7 is preferably methyl.

When X is of sub-formula (e), R_8 and R_9 are preferably both methyl groups.

When X is of sub-formula (f), and R_{10} is C_{1-6} alkoxy or is joined to Y, R_{12} is preferably amino and R_{13} is preferably chloro or bromo, most preferably chloro. R_{10} is preferably

methoxy when C_{1-6} alkoxy.

When X is of sub-formula (f), and R_{10} is hydrogen, R_{11} and R_{13} are preferably chloro or methyl and R_{10} is preferably hydrogen.

Other values of X within sub-formula (f) of interest are those described in EP-A-307172 (Eli Lilly and Company), EP-A-313393 (Yoshitomi Pharmaceutical Industries Limited), PCT/GB91/02173 and 02210 (Beecham Group p.l.c.).

When X is of sub-formula (g), R_{14} is preferably hydrogen or methyl.

When X is of sub-formula (h), and CO-Y- is in the 1-position suitable examples of R_{15} when in the 4-position, include the following: hydrogen, chloro, bromo, methyl, ethyl, amino, methylamino, dimethylamino, phenyl, C_{1-4} alkanoylamino such as formylamino, acetylamino, propionylamino, n- and iso-butyrylamino, aminosulphonyl, and amino and aminosulphonyl optionally substituted by one or two methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl or phenyl groups; nitro, n- and iso-propoxy, methylthio, ethylthio, n- and iso-propylthio, hydroxy, methylsulphonyl and ethylsulphonyl or when R_{15} is in the 3-position suitable examples, include the following groups, hydrogen, methyl, ethyl, n- or iso-propyl, methoxy, and ethoxy.

When X is at sub-formula (h), and the CO-Y- is in the 3-position, suitable examples of R_{15} when in the 1-position, include hydrogen, methyl, ethyl, n- or iso- propyl, or when R_{15} is in the 4-position, suitable examples include the following: hydrogen, methoxy and ethoxy.

Preferred R_{15} groups, in any of the positions specified above, include hydrogen, methyl and methoxy. CO-Y- is preferably in the 1-position.

Y is preferably NH.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_x-T wherein R_x is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_x include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

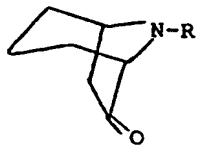
The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will also be realised that X-CO-Y- in compounds of formula (I) may adopt an α or β or configuration with respect to Z.

The compounds of formula (I) are prepared by linking together X and the azabicyclic side chain, usually by an ester or amide coupling when A is CO_2 or CONH, as described

in the aforementioned patent publication references, in particular those in the name of Beecham Group p.l.c.

The azabicyclic side chain intermediates may be prepared from the corresponding ketones of formula (II) and (III):



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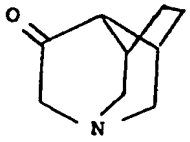


(III)

according to the methods described in the aforementioned patent references i.e. by reduction to form the corresponding alcohol, or by formation of the corresponding oxime followed by reduction, to form the corresponding amine.

The ketones of the formula (II) may be prepared according to the method described by G. H. Dewar, R.T. Parfitt, L. Sheh; Eur. J. Med. Chem., 1985, 20, 228, and the ketone of formula (III) may be prepared according to the method described in the Description 2 hereinafter.

The compounds of the present invention are 5-HT_3 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of pain, emesis, CNS disorders and gastrointestinal disorders. Pain includes migraine, cluster headache, trigeminal neuralgia and visceral pain; emesis, includes, in particular, that of preventing vomiting and nausea associated with cancer therapy, post-operative emesis, and nausea associated with migraine. Examples of such cancer therapy include that using cytotoxic agents, such as platinum complexes including cisplatin, and also doxorubicin and cyclophosphamide, particularly cisplatin;

and also radiation treatment. CNS disorders include anxiety, psychosis, cognitive disorders such as senile dementia and age associated memory impairment (AAMI), and drug dependence. Gastrointestinal disorders include irritable bowel syndrome and diarrohea.

5-HT_3 receptor antagonists may also be of potential use in the treatment of obesity, arrhythmia, and/or disorders associated with myocardial instability.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable

lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of

approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

The following Examples illustrate the preparation of compounds of formula (I); the following Descriptions relate to the preparation of intermediates.

Description 1

a) 8-Methyl-8-azabicyclo[3.2.1]octan-6-one oxime hydrochloride

To a stirred solution of the ketone (G.H. Dewar, R.T. Parfitt, L. Sheh; Eur. J. Med. Chem., 1985, 20, 228) (5.3g) in EtOH (100ml) was added hydroxylamine hydrochloride (4.0g) and the reaction was then heated on a steam bath for 1½h.

The reaction mixture was allowed to cool to room temperature, concentrated to half volume, and further cooled to -10°C. The crystals of the title compound were collected, washed with Et_2O and dried under vacuum (5.8g, 80%).

b) 6-Amino-8-methyl-8-azabicyclo[3.2.1]octane

Following the procedure outlined in Description 2f), the oxime (2.5g) was reduced with sodium in amyl alcohol to give the title compound (1.0g, 53%) isolated as the free base as a mixture of isomers.
^1H NMR ($CDCl_3$) 270MHz: 3.71, 3.30 (m, 1H), 3.17, 3.02 (m, 1H), 2.79, 2.70 (m, 1H), 2.47, 2.24 (s, 3H), 1.95-0.90 (m, 10H).

Description 2

a) 3-Benzyl-3-azabicyclo[3,2,1]octan-8-one

Cyclopentanone (126, 1.5mol) and 40% aqueous formaldehyde (340mol) were heated under reflux in glacial acetic acid (2800ml) with benzylamine hydrochloride (216g, 1.5mol) for four hours. The reaction mixture was allowed to cool to room temperature and 12N HCl (120ml) was added. The solution was concentrated on a rotary evaporator and water (400ml) added. The aqueous was washed with ethyl acetate (2 x 500ml), saturated with potassium carbonate and the product extracted into pentane (3 x 800ml) and dried (K_2CO_3). This solution was filtered through a bed of silica gel (500g) eluting with pentane/Et_2O 70:30. Distillation gave the title compound (20g, 6%) Bp 128-32°, 0.3mmHg.
^1H NMR 60MHz ($CDCl_3$) δ: 7.30 (s, 5H), 3.60 (s, 2H), 3.0-2.80 (m, 2H), 2.70-2.40 (m, 2H), 2.30-1.80 (m, 6H).

b) 3-Benzyl-8-cyano-3-azabicyclo[3.2.1]octane

The ketone (19.9g, 0.093mol) and Tosmic (23.4g, 0.12 mol) were dissolved in a mixture of dry DME (140ml) and t-butanol (70ml). The stirred solution was cooled to 0°C and potassium-t-butoxide (22g, 0.19mol) added portionwise. The

reaction was stirred for a further two hours and poured into pentane (1000ml). The mixture was filtered through Kieselguhr and evaporated to dryness. The residue was purified by flash column chromatography through tlc silica eluting with petrol/ CH_2Cl_2 75:25, to give the title compound (11.0g, 53%).

c) Ethyl-3-benzyl-3-azabicyclo[3.2.1]octane-8-carboxylate

A solution of the nitrile (11g, 0.058mole) in ethanol (80ml) and C. H_2SO_4 (20ml) was heated under reflux for 20h. The mixture was poured onto ice water (400ml) and 40% NaOH solution (60ml) added. The product was extracted into ether and the ethereal extracts washed with saturated brine, dried over Na_2SO_4 and evaporated to dryness. The residue was distilled to give the title compound (10.3g, 78%) Bpt 144-8°, 0.5mmHg.

^1H NMR, 60MHz ($CDCl_3$) δ: 7.20 (s, 5H), 4.30-3.80 (m, 2H), 3.40 (s, 2H), 2.70-1.60 (m, 11H), 1.20 (m, 3H).

d) Ethyl-3-carbethoxymethyl-3-azabicyclo[3.2.1]octane-8-carboxylate

The N-benzyl ester (10.0g, 0.037mol) was hydrogenated at atmosphere pressure in ethanol (200ml) and glacial acetic acid (25ml) over 10% Pd/C catalyst for one hour. Filtration through Kieselguhr and evaporation of the filtrate to dryness gave the NH product. A solution of the NH product, and ethyl bromoacetate (4.2ml, 0.037mol) in acetone (250ml) was stirred and heated under reflux with K_2CO_3 (16g, 0.11mol) for 16h. The reaction was cooled, filtered and evaporated to dryness. Distillation of the residue gave the title compound (6.1g, 62%) Bpt 126-8°, 0.5mmHg.

e) 6-Azatricyclo[4,3,1,$0^{4,9}$]decan-8-one oxime

The di-ester (6.1g, 0.023mol) in dry toluene (100ml) was added to a suspension of potassium-t-butoxide (6.4g, 0.057mol) in dry toluene (500ml) heated under reflux under N_2. The mixture was heated under reflux for a further three hours and allowed to cool. Dilute HCl (150ml) was added with vigorous stirring, the aqueous layer was separated and heated under reflux for 72 hours. The resulting solution was concentrated to a small volume and saturated with potassium carbonate. The product was extracted into ether (2 x 300ml), dried over Na_2SO_4 and evaporated to dryness to give the ketone (2.14g, 62%) which was then converted to the oxime derivative (1.97g, 84%) with hydroxylamine hydrochloride.

f) 8-Amino-6-azatricyclo[4,3,1,$0^{4,9}$]decane

The oxime (1.97g, 0.012mol) was dissolved in amyl alcohol (80ml) and heated to reflux under N_2. Sodium metal (6.5g, 0.28mol) was added portionwise over a 20 minute period and heating was continued for a further 1.5h. The solution was allowed to cool slightly and water (20ml) was added carefully. The aqueous layer was separated and the organic layer extracted with dilute HCl (3 x 25ml). The extract was evaporated to dryness to give the title compound (3.5g, 100%).

Example 1

(±) 4-Acetamido-5-chloro-2-methoxy-N-(8-methyl-8-azabicyclo[3.2.1]octan-6-yl)benzamide (E1)

4-Acetamido-5-chloro-2-methoxybenzoic acid (1.70g) was dissolved in thionyl chloride (8ml) and stirred at room temperature for 30 min. Petrol (15ml) was added and the precipitated acid chloride, filtered off and washed with petrol.

To a stirred solution of the acid chloride in CH_2Cl_2 (30ml) cooled to 0°C were added dropwise the amine (D8) (1.0g) and Et_3N (1.0ml). The reaction mixture was allowed to warm to room temperature and stirred overnight.

The mixture was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated under reduced pressure. The residue was chromatographed on alumina using CH_2Cl_2 to 1:1 CH_2Cl_2:$CHCl_3$ as eluant, followed by recrystallisation from EtOAc/petrol to yield the title compound (1.2g, 45%).

^1H NMR ($CDCl_3$) 270MHz δ: 8.30 (s, 1H), 8.20 (s, 1H), 8.09 (d, 1H), 7.80 (s, 1H), 4.90 (m, 1H), 3.97 (s, 3H), 3.32 (m, 1H), 3.09 (s, 1H), 2.53 (s, 3H), 2.27 (s, 3H), 2.00-1.15 (m, 8H).

Example 2

(±) 4-Amino-5-chloro-2-methoxy-N-(8-methyl-8-azabicyclo[3.2.1]octan-6-yl)benzamide hydrochloride (E2)

To a stirred solution of the amide (E2) (1.2g) in EtOH (20ml) was added NaOH (aq) (10%) (3.2ml) and the reaction heated to reflux overnight.

The reaction was allowed to cool and evaporated under reduced pressure. The residue was taken up in H_2O and the product extracted into CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure.

The residual oil was taken up in a small volume of EtOH and ethanolic HCl added. Ether was added and the precipitate filtered off, washed with Et_2O and dried under reduced pressure to yield the title compound (E2) (0.6g, 53%). m.p. 238-240°.

^{1}H-NMR (DMSO) 270MHz δ: 8.22 (d, 1H), 7.80 (s, 1H), 6.63 (s, 1H), 6.15 (s, 2H), 4.9, 4.49 (m, 1H), 3.96 (s, 3H), 3.47 (s, 3H), 2.45-1.40 (m, 10H).

Example 3

N-(6-Azatricyclo[4,3,1,$0^{4,9}$]decan-8-yl)-1-methylindazole-3-carboxamide hydrochloride (E3)

1-Methylindazol-3-oyl chloride (0.86g, 0.0044mol) was dissolved in dry CH_2Cl_2 (50ml) and the amine dihydrochloride D6 (1.0g, 0.0044mol) added followed by triethylamine (2.0ml, 0.014mol). The mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with 5% $NaHCO_3$ solution and the organic layer separated and dried (Na_2SO_4). After evaporation, the residue was purified by chromatography on silica (30g) eluting with $CHCl_3$ (0.4g, 26%). Mpt 280-2°. Treatment with ethanolic HCl afforded the title compound.

^{1}H NMR, 270MHz (DMSO-d^6) δ: 8.95 (d, 1H), 8.25 (d, 1H), 7.85 (d, 1H), 7.60-7.53 (m, 1H), 7.41-7.33 (m, 1H), 4.85-4.76 (m, 1H), 4.27 (s, 3H), 3.80-3.40 (m, 4H), 3.28-3.20 (m, 1H), 2.99-2.83 (m, 2H), 2.60-2.48 (m, 1H), 2.25-2.19 (m, 1H), 2.09-1.81 (m, 2H), 2.75-2.64 (m, 2H).

5-HT_3 Receptor Antagonist Activity

Compounds are evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

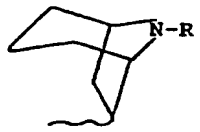
Male rats 250-350g, are anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate are recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6µg/kg) is given repeatedly by the intravenous route and changes in heart rate quantified. Compounds are given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the control response (ED_{50}) is then determined.

Claims

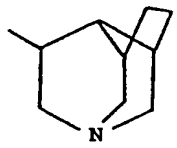
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:

X-A-Z (I)

wherein Z is of structure (a) or (b):



(a)



(b)

wherein

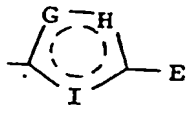
X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;

A is a linking moiety; and

R is hydrogen or methyl;

having 5-HT_3 receptor antagonist activity.

2. A compound according to claim 1 wherein A is CONH, COO, NHCONH, CONHCONH or a group of structure (j):



(j)

wherein the dotted circle represents two double bonds in any position in the 5 membered ring; two of G, H and I are selected from oxygen, sulphur, nitrogen and carbon and the other is oxygen, sulphur or nitrogen; and E is a bond or C_{1-5} alkylene optionally substituted by phenyl or hydroxy.

3. A compound according to claim 1, of formula (IA), or a pharmaceutically acceptable salt thereof:

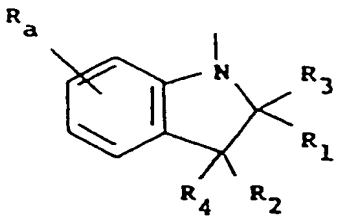
$$X_1\text{-CO-Y-}Z$$

(IA)

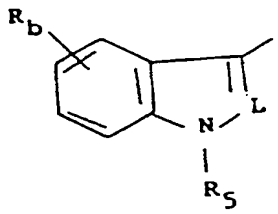
wherein

Y is NH or O (or is joined to R_{10} as defined below);

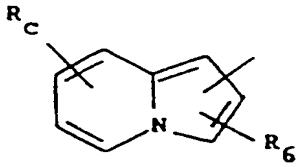
X_1 is a group of formula (a), (b), (c), (d), (e), (f), (g) or (h):



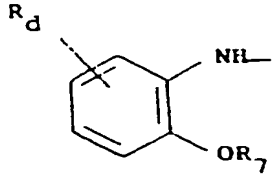
(a)



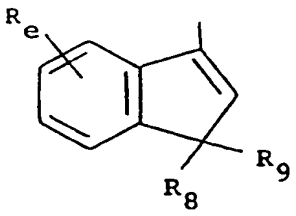
(b)



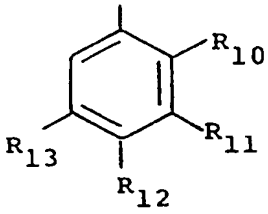
(c)



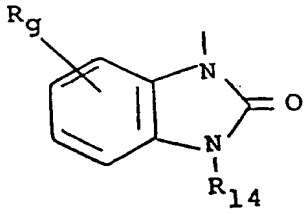
(d)



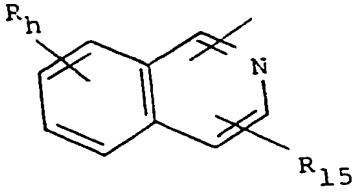
(e)



(f)



(g)



(h)

wherein

R_a to R_e and R_g to R_h are selected from hydrogen, halogen or hydroxy;

R_1 is hydrogen and R_2 is hydrogen or C_{1-4} alkyl; or

R_1 and R_2 together are a bond;

R_3 to R_7 are independently hydrogen or C_{1-6} alkyl; and

R_4 together with R_2 may be C_{2-7} polymethylene or C_{2-6} polymethylene interrupted by an -O- linkage when R_1 is hydrogen;

R_8 and R_9 are independently selected from hydrogen or C_{1-6} alkyl or R_8 and R_9 together are C_{2-6} polymethylene or C_{2-5} polymethylene interrupted by an -O- linkage;

either R_{10} is hydrogen, C_{1-6} alkoxy, C_{3-8} cycloalkyloxy or C_{3-8} cycloalkyl C_{1-4} alkyloxy; or R_{10} is joined to Y so that Y-R_{10} is N-B=N where B is N or CH; and

R_{11} is hydrogen, halo, C_{1-6} alkoxy or C_{1-6} alkyl; or

R_{10} and R_{11} are joined to form $-OCH(R_{15}R_{16})-E-$ wherein E is $(CH_2)_n$, $(CH_2)_pO\ NR_{17}CO(CH_2)m$ wherein n is 1 or 2, p is 0 or 1 and m is 0 or 1 and R_{15}, R_{16} and R_{17} are independently selected from hydrogen or C_{1-6} alkyl;

R_{12} is hydrogen, C_{1-6} alkoxy or; amino optionally substituted by a C_{1-6} alkyl group, or R_{12} is alkanoylamino; and

R_{13} is halo, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio;

R_{14} is hydrogen or C_{1-6} alkyl;

in formula (h):

CO-Y- is in the 1-position and either R_{15} is in the 3-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, phenyl optionally substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups or by C_{4-5} polymethylene or by phenyl, C_{1-6} alkylsulphonyl, C_{1-6}

alkylsulphinyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy or nitro; or

CO-Y- is in the 3-position and either R_{15} is in the 1-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen or C_{1-6} alkoxy;

L is CH or N; and

Z and R are as defined in claim 1.

4. A compound according to claim 3 wherein X is of sub-formula (a), one of R_1 and R_3 is hydrogen and R_2 and R_4 are both C_{1-6} alkyl groups or are joined to form C_{2-7} polymethylene.

5. A compound according to claim 3 wherein X is of sub-formula (b), and R_5 is hydrogen or a methyl or ethyl group.

6. A compound according to claim 3 wherein X is of sub-formula (d) and R_7 is methyl.

7. A compound according to claim 3 wherein X is of sub-formula (f) wherein R_{10} is methoxy, R_{12} is amino and R_{13} is chloro or bromo.

8. A compound according to claim 3 wherein X is of sub-formula (g) wherein R_{14} is hydrogen or methyl.

9. (±) 4-Amino-5-chloro-2-methoxy-N-(8-methyl-8-aza-bicyclo[3.2.1]octan-6-yl)benzamide.

10. N-(6-Azatricyclo[4,3,1,$0^{4,9}$]decan-8-yl)-1-methyl-indazole-3-carboxamide.

11. A pharmaceutically acceptable salt of a compound according to claim 9 or 10.

12. A compound according to claim 1, substantially as described herein with reference to any one of the Examples.

13. A process for the preparation of a compound according to claim 1 which process comprises linking together X and the azabicyclic side chain according to known methods.

14. 6-Amino-8-methyl-8-azabicyclo[3.2.1]octane.

15. 8-Amino-6-azatricyclo[4,3,1,$0^{4,9}$]decane.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12, and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition for use in the treatment of pain, emesis, CNS disorders or gastrointestinal disorders comprising an effective amount of a compound according to claim 1, and a pharmaceutically acceptable carrier.

18. A compound according to any one of claims 1 to 12, for use as an active therapeutic substance.

19. A compound according to any one of claims 1 to 12, for use in the treatment of pain, emesis, CNS disorders or gastrointestinal disorders.

20. Use of a compound according to any one of claims 1 to 12, in the manufacture of a medicament for the treatment of pain, emesis, CNS disorders or gastrointestinal disorders.

21. A method of treatment of pain, emesis, CNS disorders or gastrointestinal disorders in mammals, which comprises the administration of an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/00050

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 451/02 C 07 D 453/02 C 07 D 519/00
A 61 K 31/46 A 61 K 31/435 //(C 07 D 521/00 C 07 D 471:00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 F 451/00 C 07 D 453/00 C 07 D 519/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	Chemical Abstracts, vol. 114, 1991, (Columbus, Ohio, US), see Abstract and Chemical Substance Index, page 700, column 1, lines 62,77-79, J. FENG et al.: "A screening test for Boajiasu derivatives", see page 22, abstract no. 220761m, & SHANGHAI DIER YIKE DAXUE XUEBAO 1990, 10(4), 324-6	1,16
X	EP,A,0013138 (BEECHAM) 9 July 1980, see claim 1; pages 47-53	1,16

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
31-03-1992	20. 05. 92
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [XX] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

REMARK: ALTHOUGH CLAIM 21 IS DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200050 SA 55270

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/05/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0013138	09-07-80	AU-B- 527837	24-03-83
		AU-A- 5425579	03-07-80
		AU-B- 543825	02-05-85
		AU-A- 9135182	10-03-83
		CA-A- 1218062	17-02-87
		CA-C- 1220473	14-04-87
		EP-A,B 0081054	15-06-83
		EP-A,B 0220339	06-05-87
		JP-A- 2072178	12-03-90
		JP-A- 55092384	12-07-80
		US-A- 4273778	16-06-81
		US-A- 4336259	22-06-82
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